Cancer Risk in Users of Calcium Channel Blockers

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Abstract Ca^{2+} channel blockers may cause cancer by inhibiting apoptosis or reducing intracellular Ca^{2+} in certain tissues. Recent findings suggest that drug users are at increased risk for cancer in general and for colon cancer in particular. We conducted a study in one Danish county of 17 911 patients who received at least one prescription of Ca^{2+} channel blockers between 1 January 1991 and 31 December 1993. The patients were identified from records in the National Health Insurance Program, which refunds part of the price of such drugs. Cancer occurrence and rate were determined by use of the files of the Danish Cancer Registry and compared with county-specific incidence rates for various categories of cancer. During the follow-up period of up to 3 years, 412 cancers were observed among users of Ca^{2+} channel blockers, compared with 414 expected, to yield an age- and sex-standardized incidence ratio (SIR) of 1.00 (95% confidence interval, 0.90 to 1.10). There was no indication of an excess risk in the subgroup of likely long-term users or users of specific drugs. The SIR of colon cancer, a site of a priori interest, was 0.8 (95% confidence interval, 0.5 to 1.1) on the basis of 34 cases. Although the results are reassuring, the lack of association could reflect the relatively short follow-up after registration in the prescription database. Continued monitoring of cancer risk is planned. (***Hypertension.*** **1997;29:1091-1094.**)

Key Words • calcium channel blockers • apoptosis • neoplasms • epidemiology • cohort studies

Recently, it was hypothesized that regular use of Ca^{2+} channel blockers increases the risk of cancer.[1-4] One proposed mechanism is that calcium antagonists inhibit apoptosis, a process for destruction of aberrant cells,[5,6] thus reducing the body's natural defenses against the growth of cancer cells[7] and resulting in a tumor-promoting effect. Another possible mechanism is block of transmembranous calcium channels, causing a reduction in the intracellular Ca^{2-} content of certain tissues.[4] Whereas the first mechanism may affect cancer risk generally, the second may be relevant to specific cancer sites, eg, the colon, in which calcium turnover may play an etiologic role.[8,9]

The possibility of a generally increased cancer risk after use of Ca^{2+} channel blockers is supported by results of a recent extension[3] of a previous cancer study,[2] which in turn is based on a collaborative follow-up study of 5052 people aged 71 years or older from three regions in the United States.[10] Among 451 participants who reported use of Ca^{2+} channel blockers at baseline, 47 cancers were observed during the 4 years of follow-up, yielding a 1.7-fold increased incidence of cancer (95% confidence interval [CI], 1.3 to 2.3) compared with the incidence among cohort members not reporting use of such drugs. The association was found for most common cancers and tended to remain unchanged in drug-specific analyses (verapamil, nifedipine, and diltiazem).

These findings, along with other long-term side effects[11-14] and increased mortality[15,16] reported among Ca^{2+} channel blocker users, prompted us to examine the incidence of cancer in a population-based cohort of approximately 18 000 users in a well-defined region in Denmark. Ca^{2+} channel blockers have been widely used in the treatment of hypertension, stable or vasospastic angina, and supraventricular tachyarrhythmias since their introduction into the Danish market in the late 1960s. In 1993, around 2% of the population aged 50 years or more were being treated with these drugs.

Methods

We used the population-based Pharmaco-Epidemiological Prescription Database of the County of North Jutland, Denmark,[17] started on 1 January 1991, to identify 172 801 Ca^{2+} channel blocker prescriptions to 17 944 individuals up to 31 December 1993. During the period 1991 to 1993, the population of the County of North Jutland was around 487 000 inhabitants, representing approximately 9% of the total Danish population. The county is served by 33 pharmacies equipped with a computerized accounting system from which data are sent to the health insurance administration of the Danish National Health Service. The National Service provides tax-supported health care for all inhabitants of the country. Besides guaranteeing free access to hospitals, public clinics, and general practitioners, the insurance program refunds 50% to 75% of the costs associated with the purchase of Ca^{2+} channel blockers and other drugs prescribed by doctors.

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The information that is transferred to the Prescription Database from the accounting system maintained by the pharmacies includes the customers' personal identification number (which incorporates date of birth), the type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system,[18] and the date of the prescription.[17,19] The use of the unique 10-digit personal identification number, which is assigned to all citizens shortly after birth by the Central Population Register (CPR), ensured that a complete prescription history could be established for each participant. The prescriptions included in the present study covered verapamil (ATC code CO2D EO1), nifedipine (CO2D EO2), nitrendipine (CO2D EO5), nicardipine (CO2D EO9), felodipine (CO2D E10), amlodipine (CO2D E12), isradipine (CO2D E13), and diltiazem (CO2D EO4). In the analyses, nifedipine, nitrendipine, nicardipine, felodipine, amlodipine, and isradipine were combined into a group of dihydropyridines.

The CPR was used to determine vital status and migration. Of the 17 944 patients initially identified in the Prescription Database as users of Ca^{2+} channel blockers, 17 (0.1%) could not be found in the files of the CPR, possibly because the personal identification numbers were coded incorrectly, and 16 (0.1%) had died before or at the date of prescription. These patients were excluded, leaving 17 911 patients for study.

The study cohort was then linked to the files of the Danish Cancer Registry, which collects information on all individuals in Denmark with cancer, including benign brain tumors and bladder papillomas.[20] The follow-up period for cancer occurrence began at the date of first known prescription of Ca^{2+} channel blockers and ended at the date of emigration (n=17), date of death (n=1872), or 31 December 1993 (n=16 022), whichever occurred first. Cancers were classified according to the modified Danish version of the *International Classification of Diseases*, 7th Revision (ICD-7).[21] Nonmelanoma skin cancer was excluded from the analysis because of underreporting to the Cancer Registry.[22]

The number of cancer cases observed among individuals taking Ca^{2+} channel blockers was compared with the number of cases expected on the basis of rates from the Danish Cancer Registry, and the standardized incidence ratio (SIR) was calculated as the ratio of the observed to the expected number of cancer cases. County-specific incidence rates for all tumor categories, calculated according to sex and age (in 5-year groups), were applied to the person-years of observation to obtain the number of cancers expected had the patients experienced the same incidence rates as the general population of the county. The statistical methods used assume that the observed number of cases of cancer in any specific category followed a Poisson distribution. Tests of significance and CI for the SIR were calculated from an accurate asymptotic approximation; exact confidence limits were used if the observed numbers of cases were small.[23]

Results

For the 17 911 patients included in the survey, 32 540 person-years of follow-up were accrued (average, 1.8 years; range, >0 to 3 years). The characteristics of the cohort are shown in Table 1. Most patients were users of a single drug group—dihydropyridines (41%), verapamil (27%), or diltiazem (24%)—throughout the registration period; only 8% used drugs from more than one group. About 80% of patients included during the first study year, 1991, remained on treatment until the date of death or the end of the study on 31 December 1993.

Overall, 412 cancers were diagnosed versus 413.9 expected (Table 2), yielding an SIR of 1.00 (95% CI, 0.90 to 1.10). The SIR was 1.02 (0.89 to 1.16) for men and 0.97 (0.83 to 1.12) for women.

TABLE 1. Descriptive Characteristics of 17 911 Patients in the County of North Jutland, Denmark, Taking Ca^{2+} Channel Blockers; Prescription Data Between 1 January 1991 and 31 December 1993

Characteristic	Patients	
	Number	%
Total group	17 911	100
Men	8841	49
Women	9070	51
Year at first entry		
1991	9759	54
1992	4229	24
1993	3923	22
Age at first entry, y		
<59	5706	32
60-69	4950	28
70-79	5133	29
≥80	2122	11
Type of antagonist*		
Verapamil only	4879	27
Dihydropyridines only†	7370	41
Diltiazem only	4247	24
Mixed use	1415	8

*According to use over the study period.
†Includes amlodipine (31%), felodipine (26%), nifedipine (22%), nitrendipine (11%), isradipine (6%), and nicardipine (4%).

The numbers of patients enrolled during the first 4 months of the registration period (1 January to 30 April 1991) were 3255, 1935, 1064, and 695, respectively. Subsequently, the average monthly enrollment of new patients through 31 December 1993 was 350. The initial group of 6949 patients was assumed to include approximately 5500 prevalent users (6949−[4×350]) at the start of the Prescription Database in January 1991. In this group of potential long-term users, we found a slightly decreased risk for all cancers combined (SIR=0.95; 95% CI, 0.83 to 1.08), compared with a slight increase (SIR=1.06; 95% CI, 0.91 to 1.22) for the 11 162 patients enrolled later (Table 2). When risk was analyzed according to age at first

TABLE 2. Standardized Incidence Ratios for Total Cancer Among 17 911 Patients Taking Ca^{2+} Channel Blockers, by Sex, Year of Entry, Age at Entry, and Type of Antagonist

Patient Group	No. Observed	No. Expected	SIR	95% CI
Total group	412	413.9	1.00	0.90-1.10
Men	228	223.6	1.02	0.89-1.16
Women	184	190.3	0.97	0.83-1.12
Time of entry				
1 January to 30 April 1991	227	239.2	0.95	0.83-1.08
1 May 1991 to 31 December 1993	185	174.7	1.06	0.91-1.22
Age at entry, y				
<70	177	173.1	1.02	0.88-1.18
≥70	235	240.8	0.98	0.86-1.11
Type of antagonist				
Verapamil only	152	139.8	1.09	0.92-1.27
Dihydropyridines only*	112	128.4	0.87	0.72-1.05
Diltiazem only	108	104.0	1.04	0.85-1.25
Mixed use	40	41.7	0.96	0.69-1.31

CI indicates confidence interval.
*Includes amlodipine (31%), felodipine (26%), nifedipine (22%), nitrendipine (11%), isradipine (6%), and nicardipine (4%).

TABLE 3. Standardized Incidence Ratios for Cancer of Selected Sites Among Patients Taking Ca^{2+} Channel Blockers

Site of Cancer (ICD-7 code)*	No. Observed	No. Expected	SIR	95% CI
Digestive organs (150-159)	113	120.2	0.9	0.8-1.1
Esophagus (150)	7	4.3	1.6	0.7-3.3
Stomach (151)	12	15.8	0.8	0.4-1.3
Colon (153)	34	43.4	0.8	0.5-1.1
Rectum (154)	22	24.1	0.9	0.6-1.4
Pancreas (157)	17	14.3	1.2	0.7-1.2
Lung (162)	57	60.0	1.0	0.7-1.2
Breast (170)	32	40.3	0.8	0.5-1.1
Female genital organs (171-176)	22	27.0	0.8	0.5-1.2
Prostate (177)	39	37.8	1.0	0.7-1.4
Kidney (180)	14	13.9	1.0	0.6-1.7
Urinary bladder (181)	47	30.5	1.5	1.1-2.1
Melanoma (190)	7	9.3	0.8	0.3-1.6
Brain (193)	14	9.4	1.5	0.8-2.5
Lymphatic and hematopoietic tissues (200-205)	34	30.3	1.1	0.8-1.6
Non-Hodgkin's lymphoma (200, 202)	17	12.4	1.4	0.8-2.2
Leukemia (204)	12	11.0	1.1	0.6-1.9
Other and unspecified sites	33	35.2	0.9	0.7-1.3

SIR indicates standardized incidence ratio; CI, confidence interval.
*Modified version of the 7th *International Classification of Diseases.*[21]

prescription or according to type of Ca^{2+} channel blocker used, none of the results indicated an increase in overall cancer risk (Table 2).

Table 3 shows the site-specific risks of cancer among cohort members. The SIR for colon cancer, a site of a priori interest, was 0.8 (95% CI, 0.5 to 1.1) on the basis of 34 cases. The only statistically significant association was seen for tumors of the urinary bladder, with 47 cases observed versus 30.5 expected. The elevated risk was confined to men who received diltiazem exclusively (SIR=2.1; 95% CI, 1.2 to 3.4) or multiple Ca^{2+} channel blockers (SIR=2.6; 95% CI, 1.1 to 5.0). Among women, only 6 bladder tumors were observed versus 7.0 expected (SIR=0.9; 95% CI, 0.3 to 1.9). The SIRs were nonsignificantly elevated for brain cancer (1.5) and non-Hodgkin's lymphoma (1.4).

Discussion

The overall occurrence of cancer in individuals taking Ca^{2+} channel blockers was remarkably close to that expected from incidence rates for the general population of the study area. In particular, we found no evidence of an increased risk of colon cancer, which some epidemiological studies have linked to low dietary calcium intake[8,24] and to use of antihypertensive drugs, including Ca^{2+} channel blockers.[25,26]

Our findings differ from those of a recent follow-up study from the United States by Pahor et al,[3] who, on the basis of 47 observed cancers, reported an overall cancer risk ratio of 1.7 among users of Ca^{2+} channel blockers, with a lower 95% confidence limit of 1.27. In contrast, our study, which includes almost nine times as many cancer outcomes (412), revealed an overall SIR of 1.00 with an upper 95% confidence limit of 1.10. The reasons for the different results are unclear but may relate to methodological issues. In particular, the comparison cohort Pahor et al used was small (n=4601), with about 80% response rates.[10] The Danish study has the advantage of being able to collect information on drug use from a computerized pharmacoepidemiological prescription database[17,19,27] with a virtual 100% follow-up of study subjects for cancer using the national cancer register, thereby making selection or observational bias unlikely.[20] The introduction in Denmark in 1968 of the Central Population Register and each citizen's unique 10-digit personal identification number basically eliminates loss to follow-up or mislinkage of register information.[28]

Because of the observational nature of our study, other types of systematic errors may have influenced the validity of the results. Calcium antagonists are often prescribed to individuals who are in poorer health; bias by indication may occur if, for example, a prevalent but undiagnosed cancer aggravates cardiovascular symptoms, leading to treatment with Ca^{2+} channel blockers. Better surveillance of sick individuals with consequently more diagnostic workups is another example of potential bias. However, both of these biases would tend to overestimate the cancer occurrence among users of Ca^{2+} channel blockers.

Finally, our study is limited by a follow-up period of only 3 years, similar to the 4 years of follow-up in the study by Pahor et al.[3] Both follow-up periods may be too brief to measure a carcinogenic effect, even if the drugs act as tumor promoters. We attempted to address this problem in part by stratifying the cohort members into prevalent users and new patients. No evidence of an excess cancer risk was found in more than 5500 prevalent users with longer periods of exposure.

The significantly increased risk observed for bladder cancer was evident only among males using diltiazem or multiple Ca^{2+} channel blockers. We have no plausible explanation for this finding other than it is a result of multiple statistical testing; we tested 16 types of cancer, in both men and women, against each of three types of calcium antagonists. Given 96 such comparisons and our practice of establishing significance with 95% CIs, on average by chance alone we might observe approximately two "significant" positive findings. We in fact observed one positive association.

In summary, our study of Ca^{2+} channel blockers revealed no evidence of a tumor-promoting effect. Although the results are reassuring, further studies with longer follow-up are needed to fully evaluate any potential carcinogenic risk associated with these drugs.

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